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Trisomy 15 Mosaicism and Uniparental Disomy (UPD) in a Liveborn Infant

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We describe a liveborn infant with uniparental disomy (UPD) with trisomy 15 mosaicism. Third trimester amniocentesis yielded a 46,XX/47,XX,+15 karyotype. Symmetrical growth retardation, distinct craniofacies, congenital heart disease, severe hypotonia and minor skeletal anomalies were noted. The infant died at 6 weeks of life. Peripheral lymphocyte chromosomes were "normal" 46,XX in 100 cells. Parental lymphocyte chromosomes were normal. Skin biopsy showed 47,XX,+15 in 80% of fibroblasts and results were equivalent in fibroblasts from autopsy lung tissue. Molecular analysis revealed maternal uniparental heterodisomy for chromosome 15 in the 46,XX cell line. We describe an emerging phenotype of trisomy 15 mosaicism, confirm that more than one tissue should be studied in all cases of suspected mosaicism, and suggest that UPD be considered in all such cases.

KEY WORDS: uniparental heterodisomy, mosaicism, trisomy 15

INTRODUCTION

Trisomy 15 is rare in a liveborn and has been reported once in an infant who died on the fourth day of life [Coldwell et al., 1981]. Prenatal diagnosis of mosaic trisomy 15 without double aneuploidy has been reported [Gimelli et al., 1983; Bennett et al., 1992; Sundberg et al., 1994], only once culminating with a live birth [Lahdetie and Lakkala, 1992]. Double aneuploidy involving mosaic trisomy 15 has been described in two living children [Stallard and Sommer, 1989; Fryns et al., 1993]. We describe a liveborn infant with uniparental disomy (UPD) in association with trisomy 15 mosaicism.

CLINICAL REPORT

KC was a 1,700 g, 38-wk female infant born to a 32-year-old G4,P2,A2 mother via precipitous vaginal delivery. Mother was healthy except for mitral valve prolapse with moderate mitral regurgitation. Pedigree analysis showed an unrelated couple of English, Irish, and French-Canadian descent. Previous pregnancies resulted in an ectopic pregnancy, a healthy girl, and a blighted ovum. The family history was unremarkable.

Intrauterine growth retardation (IUGR) was noted on prenatal ultrasound. Subsequent amniocentesis at 30.5 weeks' gestation showed trisomy 15 mosaicism, with 4 out of 9 colonies being 47,XX,+15. A prior maternal serum triple screen at 16 wks indicated a low unconjugated estriol value of 0.38 MOM. At birth, the placenta was small but looked healthy. Birth weight was 1,700 g, length 41 cm, and OFC 29 cm (all measurements <5th percentile). Apgars were 4, 8, and 9 at 1, 5 and 10 minutes, respectively. Bag and mask ventilation was needed, and Narcan was given because of respiratory depression. Two hours after birth, the baby developed some respiratory distress, and at 5 hours, apneic episodes began. Abnormal facial features (Fig. 1) included a triangular face, relative telecanthus (inner canthal distance 2.3 cm), laterally prominent eyebrows, a large anterior fontanelle, high forehead, bitemporal receding hairline, epicanthal folds, short bulbous nose, broad, flat nasal bridge, upturned nasal tip with anteverted nostrils, long philtrum, small mouth and tongue, micrognathia, low set posteriorly angulated ears, and bilateral helical ear pits. No colobomas or cataracts were seen. The palate was high-arched without a cleft. Neck exam showed a nuchal fold. The sternum was short and the nipples were widely set. Heart exam showed regular rate and rhythm, normal S1, single S2, and a 2/6 systolic murmur heard throughout the precordium. KC had a two-vessel umbilical cord. External genitalia were normal and the anus was patent and anteriorly placed. Palmar and plantar creases were normal. Digits showed slight distal tapering with hypo-

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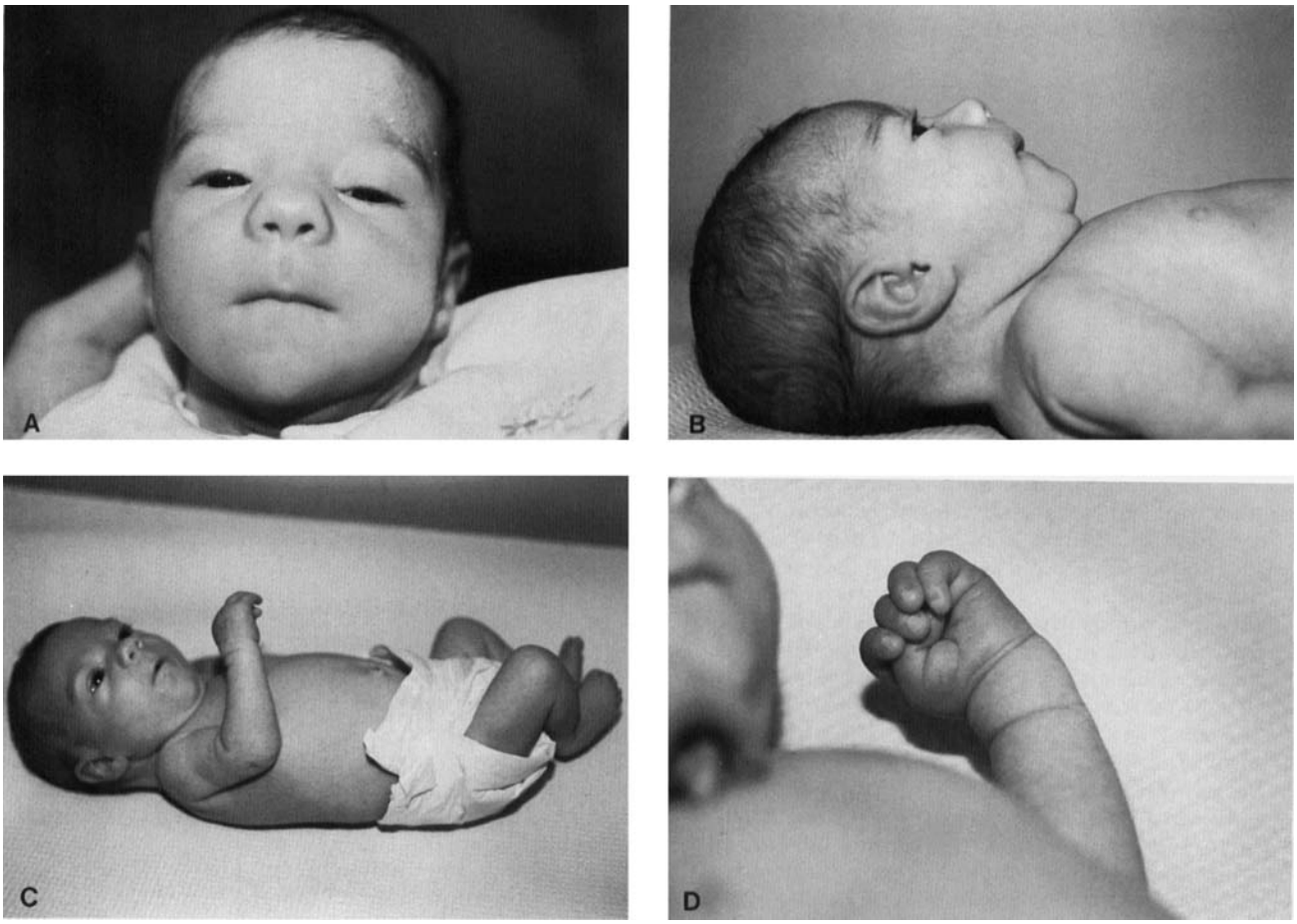

Fig. 1. Female infant with mosaic trisomy 15 particularly showing: **A,** short bulbous nose, broad, flat nasal bridge, anteverted nostrils, long philtrum, small mouth and telecanthus; **B,** low-set posteriorly angulated ear, helical pit, and micrognathia; **C,** facial findings, bitemporal receding hairline, and excess nuchal folds; and **D,** overlapping fingers with hypoplastic nails.

plastic nails and overlapping fingers (second/third and fifth/fourth). Thumbs were adducted. Excess creases were seen on all extremities. Overlapping toes (fourth/fifth and second/first) accompanied broad halluces. Joints were hypermobile with no hip clicks. Neurologic exam was significant for ptosis (left > right), decreased spontaneous movement, good suck, symmetrical Moro response, and a weak abnormal cry.

An echocardiogram showed an inlet ventricular septal defect (VSD), patent ductus arteriosus (PDA), dilated coronary sinus, and an abnormally long and redundant tricuspid valve. Four extremity blood pressures were normal.

Initial head ultrasound study showed a two-millimeter left choroid plexus cyst, a small, grade I intraventricular hemorrhage bilaterally, some calcification of the lenticular striate vessels, a present corpus callosum, and no cerebellar abnormality. KC had no seizures. She failed auditory brainstem responses (ABR) bilaterally and had abnormal visual-evoked potentials. Ophthalmologic evaluation showed no cataract, but found anomalous appearing discs which were slightly pale, large pigment crescents bilaterally, and flame hemorrhages bilaterally.

Skeletal survey showed delayed ossification centers and normal long bones. The acetabular angles were steep with questionable hip dysplasia, but with no subluxation of the hips. The ribs were thin and there were 13 bilaterally, with no vertebral anomalies noted. Renal ultrasound showed normal kidney size (4 cm) and position. Abdominal ultrasound showed normal appearing liver, spleen, and adrenals.

KC initially was a slow feeder and was tube-fed. By her second week of life she was able to feed well. She was discharged home in stable condition, with no signs of cyanosis on room air. She died at 6 weeks of life from cardiorespiratory complications secondary to a viral pneumonia. Autopsy revealed congenital heart disease with bilateral superior vena cava (left side draining into right atrium via a dilated coronary sinus); coronary arteries arising from two ostia within the aortic sinus; patent foramen ovale (3 × 2 millimeters); and two ventricular septal defects (a membranous pinpoint defect and a musuclar 1 × 1 millimeter defect). An absent

right umbilical artery and a floating cecum were noted. Mild atrophy of the optic chiasm was the only anomaly noted on neuropathological study.

MOLECULAR AND CYTOGENETIC INVESTIGATION

A karyotype of amniotic fluid cells at 30.6 weeks gestation showed 46,XX/47,XX,+15 mosaicism. Trisomy 15 was found in four independent cultures in 4/9 colonies (44%). Parental lymphocyte chromosomes were normal. Postnatal lymphocyte chromosomal analysis done on the infant was "normal," 46,XX in 100 cells. A skin biopsy showed 47,XX,+15 in 40/50 (80%) cells, as did cultivated autopsy lung tissue in 17/20 (85%) cells. The remaining cells were 46,XX. Molecular analysis of the infant's blood indicated maternal uniparental heterodisomy for chromosome 15 in the 46,XX cell line. Molecular analysis of the parental origin of the infant's chromosome 15 pair was performed as described using four polymorphic dinucleotide markers: Mfd 49 (D15S87) [Weber et al., 1990], GTAT 1B2 (D15S165) and GATA 8C05 (D15S130) [Weissenbach et al., 1992], and GATA 8B06 (D15S217) [Donlon and Morton, 1993], the first three of which were uninformative (data not shown). D15S217 results showed that the infant's fibroblasts have the three parental alleles expected for trisomy 15, but her lymphocytes manifested maternal uniparental heterodisomy from apparent maternal meiosis I nondisjunction (Fig. 2). Crossing over and recombination followed by a meiosis II nondisjunction error could also have occurred. Paternity was confirmed using several X-linked short tandem repeats (STRs) from the dystrophin gene: STR-50, STR-49, STR-45, and STR-44 [Clemens et al., 1991].

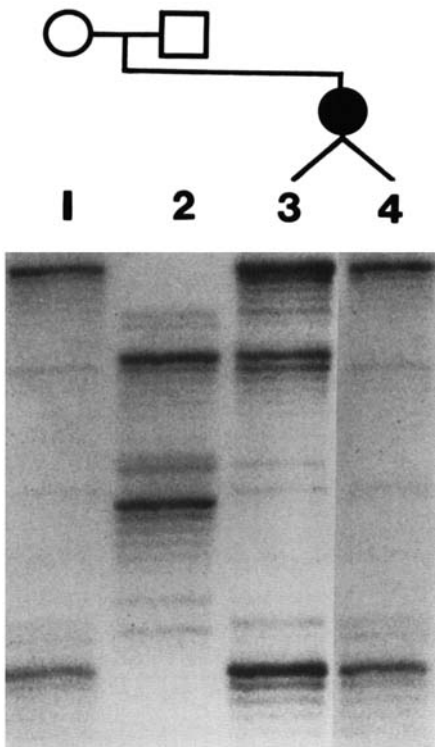

Fig. 2. Analysis of (CA)n repeat polymorphisms on chromosome 15. Polymerase chain reaction (PCR) products amplified from locus GATA 8B06 (D15S217) were size-fractionated on a 6% polyacrylamide DNA sequencing gel. Infant's DNA from fibroblasts (**lane 3**) has 2 maternal alleles and 1 paternal allele, but infant's DNA from lymphocytes has 2 maternal alleles only (**lane 4**).

DISCUSSION

Coldwell et al. [1981] described an infant with nonmosaic trisomy 15 who died in the neonatal period. Major findings in that infant included hypotonia, microcephaly, broad depressed nasal bridge, low-set ears, a VSD, coarctation of the aorta, and skeletal anomalies including 11 pairs of ribs, bilateral talipes, and congenital dislocation of the hips.

Partial trisomy 15q1 and 15q2 has been well described in the literature [Fujimoto et al., 1974; Castel et al., 1976; Turleau et al., 1977; Zabel and Baumann, 1977; Tzancheva et al., 1981]. 15q1 trisomy is characterized by an oval face, high cheek bones, deep orbits, seizures, and severe mental retardation. 15q2 trisomy is characterized by microdolichocephaly, narrow palpebral fissures, protuberant philtral borders, micrognathia, congenital heart disease including ASD, VSD, and pulmonary stenosis, and severe mental retardation.

Gimelli et al. [1983] performed prenatal diagnosis, fetal pathology studies, and cytogenetic analysis of a 46,XX/47,XX,+15 mosaic fetus. Major features in that 24-week gestational age fetus and in those of other mosaic trisomy 15 cases are documented in Table I. The neuropathological examination of the brain was normal. The mosaicism was detected following two amniocenteses and subsequently on five fetal tissues in varying percentages.

Bennett et al. [1992] described a fetus conceived through IVF with an abnormal maternal serum triple screen at the 16th week and diagnosed with trisomy 15 mosaicism via cordocentesis (Table I).

Sundberg et al. [1994] reported on a fetus with trisomy 15 mosaicism detected by amniocentesis at 12 weeks. Severe heart malformations including mitral atresia with VSD and a hypoplastic left heart were noted on echocardiography (Table I). The mosaicism was detected in amniocentesis, cordocentesis and fetal skin biopsy. The highest percentage of trisomic cells was seen in fetal skin.

Lahdetie and Lakkala [1992] detected mosaic trisomy 15 by amniocentesis at 16 and 19 weeks. The infant had IUGR and was delivered by cesarean section at 37 weeks' gestational age while in the breech position. Echocardiography revealed a hypoplastic left ventricle, mitral atresia, subvalvular aortic stenosis, a PDA, ASD, and VSD (Table I). The infant died at 13 days of age. A cord blood sample revealed a normal karyotype. Samples from extra-embryonic tissues showed varying percentages of mosaicism. A postmortem skin culture failed to grow.

Stallard and Sommer [1989] described a two-year-old with mosaic trisomy 15, doubly aneuploid for 45,X in blood and skin (Table I).The infant was lost to follow-up.

TABLE I. Major Findings in 8 Cases of Mosaic Trisomy 15

	Gimelli et al. [1993][a]	Stallard and Sommer [1989]	Lahdetie and Lakkala [1992]	Bennett et al. [1992][a]	Fryns et al. [1993]	Sundberg et al. [1994][a]	Rocklin et al. [1994][a]	Present case
Intrauterine growth retardation	−	−	+	−	+	−	−	+
Microcephaly	−	−	−	+	−	−	−	+
Craniofacial dysmorphism								
Hypertelorism	+	−	−	+	−	−	−	+
Epicanthal folds	+	+	−	−	+	−	−	+
Broad nasal bridge	−	+	−	−	+	−	−	+
Short bulbous nose	−	−	−	+	+	−	−	+
Long philtrum	−	+	−	−	+	−	−	+
Small mouth	−	−	−	−	+	−	−	+
High-arched palate	−	+	−	+	−	−	−	+
Ear anomalies	+	−	−	+	−	−	−	+
Micrognathia	+	−	−	−	+	−	−	+
Bitemporal low hairline	+	−	−	−	+	−	−	+
Short neck/nuchal fold	+	−	−	+	+	−	−	+
Skeletal/extremity defects	+	−	−	+	+	−	−	+
Heart defects	+	−	+	−	+	+	−	+
Abnormal development	NA	+	NA	NA	+	NA	NA	+
Absent spontaneous movement	NA	−	+	NA	+	NA	NA	+
Feeding problems	NA	+	NA	NA	+	NA	NA	+

[a]Fetuses were electively terminated.
+, positive finding; −, not noted.
NA, not applicable.

Fryns et al. [1993] described a newborn with trisomy 15 mosaicism and double aneuploidy (47,XX,+15/47,XXX). They proposed a specific phenotype associated with trisomy 15 mosaicism that included distinct craniofacial appearance, severe hypotonia, and other findings suggestive of the fetal akinesia sequence (Table I). The patient also had a VSD. Lymphocyte chromosomes showed 47,XXX panels in all cells and in skin biopsy a mosaic karyotype [47,XX,+15/47,XXX] was found.

Rocklin et al. [1994] reported mosaicism for trisomy 15 detected by amniocentesis and confirmed on fetal tissues at autopsy. A two-vessel cord and malrotation of the bowel were the only abnormal findings (Table I). Molecular studies indicated maternal uniparental heterodisomy in the trisomic cells.

Our patient [Milunsky et al., 1994] is unique for two reasons. She is the first liveborn trisomy 15 mosaic without double aneuploidy to survive the neonatal period. To our knowledge, this is the first liveborn infant described with mosaic trisomy 15 and uniparental disomy. In comparing our patient to the cases of trisomy 15 mosaicism previously reported, a spectrum of similar anomalies is recognized. The majority have some degree of IUGR. The craniofacial dysmorphism in our patient (Table I) is present in varying degrees in other patients described [Coldwell et al., 1981; Gimelli et al., 1983; Stallard and Sommer, 1989; Bennett et al., 1992; Fryns et al., 1993]. Congenital heart disease, especially VSD, has been documented in every case except for Bennett et al. [1992] and Stallard and Sommer [1989]. Our patient and those reported by Gimelli et al. [1983] and Coldwell et al. [1981] had some minor skeletal anomalies, specifically an abnormal rib number. Our patient had significant hypotonia with decreased spontaneous movement and an abnormally weak to absent cry. This was also observed by Coldwell et al. [1981], Fryns et al. [1993], and Lahdetie and Lakkala [1992], where the patient was born in breech position. A floating, mobile cecum was also seen in both our patient and that described by Gimelli et al. [1983]. Additional studies in our patient included a normal renal and abdominal ultrasound. Initial auditory brainstem responses and visual-evoked potentials were abnormal, but follow-up tests would have been necessary to further clarify her visual and auditory acuity.

The phenotype of trisomy 15 mosaic may now be recognized by typical craniofacial appearance, congenital heart disease, severe hypotonia, and minor skeletal anomalies. Partial trisomy 15 has been associated with severe mental retardation. Stallard and Sommer [1989] noted developmental delay in their two-year-old patient. The intellectual outcome in patients with trisomy 15 mosaicism remains unclear, but the severe mental retardation seen in partial trisomy 15 should be considered in genetic counseling.

One noteworthy feature in our patient is the presence of uniparental heterodisomy in the infant's lymphocytes, in the 46,XX cell line. Our patient does not appear to have findings that would be considered distinctive for the Prader-Willi syndrome (PWS), but some features overlap. Since ours is the first liveborn with mosaic trisomy 15 and documented UPD, the degree of

contribution of UPD to the phenotype remains uncertain. Another important but not unique observation is the problem of detecting mosaicism. In our patient, lymphocyte chromosomes were "normal," while skin fibroblasts demonstrated the mosaicism in a high percentage (80%). A similar situation was seen by Pletcher et al. [1994] describing postnatal confirmation of prenatally diagnosed trisomy 16 mosaicism. The mosaicism was confirmed postnatally in two phenotypically abnormal infants in skin fibroblasts, while their lymphocyte chromosomes were normal. It is interesting to note that in the two liveborn infants with mosaic trisomy 15, lymphocyte chromosomes were normal [Lahdetie and Lakkala, 1992; present case], while Sundberg et al. [1994] on cordocentesis found only low level mosaicism. This confirms that more than one tissue should be studied in all cases of suspected mosaicism and that UPD should be considered in all such cases.

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